Amendments to the Specification

Please amend the Brief Description of the Drawings, at page 8, lines 22 to page 10, line 31 as follows.

FIG. 1 provides VH, D and JH regions of antibody genes from B-CLL cells of Sets I-VIe. In FIG. 1-1, the germline sequences along the top are SEQ ID NO:1 and 2 (V_H4-39), SEQ ID NO:3 and 4 (D6-13) and SEQ ID NO:5 and 6 (J_H5). The sequences of the individuals in FIG. 1-1, from top to bottom, are SEQ ID NO:7-18, respectively. In FIG. 1-2, the germline sequences along the top are SEQ ID NO:19 and 20 (V_H4-34), SEQ ID NO:21 and 22 (D5-5) and SEQ ID NO:23 (J_H6 DNA sequence). The sequences of the individuals in FIG. 1-2, from top to bottom, are SEQ ID NO:24-33, respectively. In FIG. 1-3, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-02), SEQ ID NO:36 and 37 (D6-19) and SEQ ID NO:38 and 39 (J_H4). The sequences of the individuals in FIG. 1-3, from top to bottom, are SEQ ID NO:40-53, respectively. In FIG. 1-4, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-03), SEQ ID NO:55 and 56 (D6-19) and SEQ ID NO:38 and 39 (J_H4). The sequences of the individuals in FIG. 1-4, from top to bottom, are SEQ ID NO:57-74, respectively. In FIG. 1-5, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-69), SEQ ID NO:75 and 76 (D3-16) and SEQ ID NO:77 and 78 (J_H3). The sequences of the individuals in FIG. 1-5, from top to bottom, are SEQ ID NO:79-88, respectively. In FIG. 1-6, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-69), SEQ ID NO:89 and 90 (D3-10) and SEQ ID NO:91 (J_H5 DNA). The sequences of the individuals in FIG. 1-6, from top to bottom, are SEQ ID NO:92-99, respectively. In FIG. 1-7, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H3-

21) and SEQ ID NO:100 and 101 (J_H6). The sequences of the individuals in FIG. 1-7, from top to bottom, are SEQ ID NO:100-115, respectively. In FIG. 1-8, the germline sequences along the top are SEQ ID NO:1 and 2 (V_H5-51), SEQ ID NO:36 and 37 (D6-19) and SEQ ID NO:38 and 39 (J_H4). The sequences of the individuals in FIG. 1-8, from top to bottom, are SEQ ID NO:116-128, respectively. In FIG. 1-9, the germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-02), SEQ ID NO:36 and 37 (D6-19) and SEQ ID NO:54 (J_H4 DNA). The sequences of the individuals in FIG. 1-9, from top to bottom, are SEQ ID NO:40-53 and 129-159, respectively.

FIG. 2 shows amino acid alignments of the H chain V regions of all sequences in Sets II, IV, V, VIa-e, and VIII. A period indicates homology with the germline gene. Amino acids in gray are chemically similar to the germline-encoded residues. Underlined positions are known sites of allelic polymorphism. The consensus sequence for the set is shown at the bottom of each alignment. The sequences, from top to bottom, are SEQ ID NO:160-220, respectively.

FIG. 3 shows amino acid alignments of the L chain variable regions of all sequences in Sets II, IV, V, VI, and VIII. See FIG. 2 description above. The sequences, from top to bottom, are SEQ ID NO:221, 222, 221, 223, 221, 224-231, 230, 232, 231, 233-236, 236, 237, 236, 233, 236, 239 and 236, respectively.

FIG. 4 shows amino acid and nucleotide sequences of the CDR3 and its junctions of set IV. The H chain sequences are shown at left, and the L chain sequences are shown at right. The most similar germline genes are shown at top. Dots indicate

homology with the germline sequence. Dashes indicate no sequence at that position. The numbering at bottom is for convenience of reference and is arbitrary. Sequences from the public databases have their GenBank accession number in parenthesis below the case ID. Distinctive junctional residues exist, including a pair of G codons at the VH-D junction and an N codon at the D-JH junction. The creation of the G codon at the VH-D junction required trimming of the 3' adenosine nucleotide at the end of *IgVH*, along with N addition. Also, limited trimming at the 5' end of the *D* segment eliminated the first of the pair of Y codons in all cases. In two instances, D replaced Y and in two other cases N does the same; both of these are charged residues that fit at the negative end of the Kyte-Doolittle scale. The Y codon at the 3' end of the *D* gene was also eliminated in all sequences of this set. Collectively, these conserved junctional adjustments suggest strong selection for HCDR3 structure. Three rearranged L chain sequences were available for this set and both contained the *VκA27* gene associated with *Jκ1, Jκ4,* or *Jκ5*. The germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-69), SEQ ID NO:75 and 76 (D3-16), SEQ ID NO:77 and 78 (J_H3), SEQ ID NO:240 and 241 (V_KA27) and SEQ ID NO:242 and 243 (J_K1/4/5). The sequences of the individuals on the left side of FIG. 4, from top to bottom, are SEQ ID NO:79-82, 244, 245 and 83-88, respectively. The sequences of the individuals on the right side of FIG. 4, from top to bottom, are SEQ ID NO:246-251, respectively.

FIG. 5 shows amino acid and nucleotide sequences of the CDR3 and its junctions of Set VIII. The VH-D junctions are dominated by non-templated Gs. The D-JH junction exhibits evidence of trimming and fill-in, with an alteration to M where

the final *D* encoded residue would be found. This is not a known site of polymorphism, although that explanation cannot be excluded. Only one L chain sequence was available for this set (GO13), and this consisted of the *VκL6* and *Jκ3* genes. There was significant overlap between the germline segments at the VL-JL junction. The germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-69), SEQ ID NO:252 and 253 (D2-2), SEQ ID NO:23 (J_H6 DNA); SEQ ID NO:254 and 255 (V_KL6) and SEQ ID NO:256 and 257 (J_K3). The sequences of the individuals on the left side of FIG. 5, from top to bottom, are SEQ ID NO:258-262, respectively. The sequences of the individuals on the right side of FIG. 5, from top to bottom, are SEQ ID NO:263 and 264, respectively.

FIG. 6 shows amino acid and nucleotide sequences of the CDR3 and its junctions of Set V. In these sequences, the 5' end of the germline *D* gene overlaps the 3' end of the germline *IgVH* segment to form the VH-D junction. The presence of several nucleotides that do not match either germline sequence in the overlap region suggests that trimming and addition occurred, resulting in a preferred insertion of a residue with a small (A, S, and V) or no (G) side chain. The amino acids at the D-JH junction are not well conserved. However, the consistent relative positioning of the *VH*, *D*, and *JH* segments is intriguing because the region of overlap between the *VH* and *D* does not contain significant homology as might be predicted for preferential recombination. This suggests selection for HCDR3 configuration and D-encoded residues rather than specific junctional residues. Two rearranged L chain sequences were available from this set (RF22 and GN12) and both were comprised of *Vλ*1.16 (*1c*) and *Jλ1* segments. The level of mutation of both the H and L chains in the members of sets IV, V, and VIII was always

<2%, which is consistent with published reports of the frequent lack or scarcity of mutations in the *VH1-69* in B-CLL (Kipps et al., 1989; Schroeder et al., 1994; Fais et al., 1998). The germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-69), SEQ ID NO:89 and 90 (D3-10), SEQ ID NO:23 (J_H6 DNA), SEQ ID NO:265 and 266 (V_λ1-16) and SEQ ID NO:267 and 268 (J_λ1/3). The sequences of the individuals on the left side of FIG. 6, from top to bottom, are SEQ ID NO:269-274 and 93-99, respectively. The sequences of the individuals on the right side of FIG. 6, from top to bottom, are SEQ ID NO:275-278, respectively.

FIG. 7 shows amino acid and nucleotide sequences of the CDR3 and its junctions of Set II. The H chain junctions of the sequences in this set of five cases are quite constrained. The position of the *D* (*D5-5*) relative to both *VH* (*VH 4-34*) and JH (*JH6*) segments is identical for each member, leading to equal HCDR3 lengths. The VH-D and D-JH junctions both contain evidence of trimming and addition. These processes produced an aromatic residue (W, Y, F) at the VH-D junction (position 5) followed by a hydrophobic residue (G, P, or A at position 6) and a pair of codons encoding basic residues (K or R) at the D-JH junction (positions 12 and 13). At position 9 in the D segment, four out of the five HCDR3 sequences exhibit a P rather than an A found in the canonical *D5-5* segment deposited in the public databases. Although this is most likely a polymorphism of the *D5-5* segment rather than a common mutation, the last of the five sequences in this set (CLL ID47) also deviates from the canonical *D5-5* sequence at this codon, substituting a D. These highly conserved alterations of the VH-D-JH junctions suggest selection for a very particular HCDR3 structure. The rearranged L chains of this set are also very similar. All three available VLJL sequences use *VκA17* and

either *Jκ1* or *Jκ2*. The junctions are highly similar with only a single difference that results from an abbreviated recombination that eliminates the junctional P from CLL240. These cases are of the IgG isotype. Like most IgG^+ B-CLL cases that express a switched isotype (Fais et al., , 1998; Hashimoto et al., 1992; Ghiotto et al., 2004), these cases exceed the 2% difference from germline, albeit slightly, and are thus classified as mutated. The germline sequences along the top are SEQ ID NO:19 and 20 (V_H4-34), SEQ ID NO:21 and 22 (D5-5), SEQ ID NO:23 (J_H6 DNA), SEQ ID NO:279 and 280 (V_KA17) and SEQ ID NO:281 and 282 (J_K1/2). The sequences of the individuals on the left side of FIG. 7, from top to bottom, are SEQ ID NO:24 to 33, respectively. The sequences of the individuals on the right side of FIG. 7, from top to bottom, are SEQ ID NO:283-286, 283 and 287, respectively.

FIG. 8 shows amino acid and nucleotide sequences of the CDR3 and its junctions of set VI. The *VH1- 02* germline sequence is shown. There are no sequence differences between *VH1-02* and *VH1-03*, *1-18*, *1-46,* or *5-51* for the displayed region. The *Jκ1* gene is shown, and homology between CLL011 and CLL-412 and *Jκ2* at positions where the germline sequence of *J κ2* and *J κ1* are different is indicated with an asterisk. This set is composed of five subsets, totally 22 patients that share HCDR3 and VLJL characteristics but incorporate different *IgVH* genes (*1-02, 1-03, 1-18, 1-46,* and *5-51*). Each of these genes belongs to the same *VH* clan (Kirkham et al., 1992). The HCDR3 of these subsets all share a precise VHD overlap. Curiously, the *D6-19* segment was used in a nonproductive reading frame. However, this stop codon was in the region of overlap with the terminal *IgVH* sequence and was trimmed, thereby allowing productive rearrangements

with the *JH4* segment. The D-JH junctions contain evidence for trimming and addition. The first nongermline templated codon after the *D* segment is enriched in redundant L codons, but the remaining junctional codons are not tightly conserved. All the rearranged L chains available for this set use the *Vκ O12/2* gene with *Jκ* use restricted to *Jκ1* and *Jκ2*. Of these 10 sequences, 9 are essentially identical to that of the germline in the LCDR3 and junctional regions. Thus, this set is unified not only by its common HCDR3 structure and motifs but also by the use of a virtually identical VLJL partner with a very restricted LCDR3 composition. The germline sequences along the top are SEQ ID NO:34 and 35 (V_H1-02), SEQ ID NO:36 and 37 (D6-19), SEQ ID NO:38 and 39 (J_H4), SEQ ID NO:288 and 289 (V_KO12/02) and SEQ ID NO:281 and 282 (J_K1/2). The sequences of the individuals on the left side of FIG. 8, from top to bottom, are SEQ ID NO:40, 41, 44, 45, 42, 43, 46-53, 57-64, 71-74, 69, 70, 67, 68, and 116-128, respectively. The sequences of the individuals on the right side of FIG. 6, from top to bottom, are SEQ ID NO:290-295, 294, 296-298, 294, 295, 294, 291, 294, 295, 288, 290, 299 and 300, respectively.

Please enter the Sequence Listing attached hereto in paper form as **Exhibit 2** (87 pages) and in computer readable form (CRF) on floppy disk as the Sequence Listing for the subject application.

Declaration

The Notification indicates that an oath or declaration of the inventors is missing, and that a late declaration surcharge of $65.00 is required.

Accordingly, applicants attach as **Exhibit 3** a signed Declaration (9 pages) for the subject application in compliance with 37 C.F.R. §§1.497(a) and (b), identifying the application by international application number and international filing date. Applicants further enclose herewith a check for $65.00 for the late declaration surcharge.

Sequence Listing

The June 24, 2008 Notification also indicates that the application fails to comply with the requirements of 37 CFR 1.821-1.825. In response, Applicants enclose herewith a Sequence Listing in both computer readable form (floppy disk) and paper form (87 pages) (**Exhibit 2**) for the subject application. The Sequence Listing information recorded in computer readable form and attached hereto is identical to the paper copy of the Sequence Listing attached hereto. Furthermore, the Sequence Listing includes no new matter.

Applicants have also amended the specification to insert sequence identification numbers, where appropriate.

Conclusion

No fee, other than the $65.00 surcharge for a late declaration, is deemed necessary in connection with the filing of this Amendment in Response to June 24, 2008 Notification to File Missing Requirements Under 35 U.S.C. §371 in the United States

Designated/Elected Office (DE/OE/US). A check for that amount is enclosed herewith. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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